## RESPONSE

The examiner states in the Office Action Summary that claims numbered 1-37 are pending in the application and are rejected. Applicants have amended claim numbered 1, 7-8, 10-12, 15, 25, 27, 32, and 35 and canceled claim numbers 5, 6, 9, and 13. Claims numbered 1-4, 7-8, 10-12, and 14-37 will be pending upon entry of this amendment.

## SEQUENCE LISTING

Applicant respectfully submits sequence identifiers are not required for this application. Applicant directs the examiners attention to MPEP 2421.02, wherein the requirements of the sequence rules are summarized. Specifically paragraph 2, which states in part "The sequence rules embrace ...all unbranched, non-D amino acid sequences with four or more amino acids, *provided that there are at least 4 "specifically defined" ... amino acids*" (emphasis added). The present application does not disclose or claim amino acid sequences having 4 or more "specifically defined" amino acids. Furthermore, the amino acid sequences of human growth hormone, insulin, GLP-1, GLP-2, Factor VIIa, Factor VIII, EPO, glucagon, IL-2, interferon-$\alpha$ and interferon-$\beta$, referred to in the specification, are known in the art and would not further the USPTO goals of building a comprehensive data base or properly assessing the prior art.

Applicant believes the meaning of the terms "B28" and "B29" is clear as stated. Applicant respectfully submits the terms "B28" and "B29" represent standard nomenclature used when referring to insulin, and these terms are readily understood by those familiar with the technology to be insulin B-chain amino acid residues number 28 and 29.

## OBJECTIONS TO THE CLAIMS

The Examiner has objected to the recitation of RP-HPLC (claims 27-31), GLP-1 (claims 32-34), and GLP-2 (claim 32).

Applicants submit that these objections have been obviated by the insertion of the full terminology into claims 27 and 32. Withdrawal of the objections is respectfully requested.

**REJECTIONS UNDER 35 USC §112, 2nd paragraph**

The Examiner has rejected claims 1-37, now 1-5, 7-8, 10-12, and 14-37 , under 35 USC §112, 2nd paragraph, for improper Markush language and claim 12 for its confusing dependency.

Applicants submit that this rejection has been obviated by the insertion of "the group consisting of" into the appropriate claims. Withdrawal of this rejection is respectfully requested.

The rejection of claim 12 has been obviated by amending the claim to depend only from claim 1. Withdrawal of this rejection is respectfully requested.

**REJECTIONS UNDER 35 USC §103(a)**

The Examiner has rejected claims 1-37, now 1-5, 7-8, 10-12, and 14-37 , under 35 USC §103(a) as being obvious over WO 2000/55119 (Hansen) in view of Zivanovic et al [Biomedical Chromatography 14:56-57 (2000)] (Zivanovic). Applicants respectfully submit that this rejection has been obviated by appropriate amendment.

As noted on page 7 of the present Office Action, the primary differences between the presently claimed process and that of Hansen is the small amount of polar solvent used in the presently claimed process and the presence of an acid in the presently claimed process. In order to further clarify the presently claimed invention, Applicants have incorporated the aprotic polar solvent and acid limitations of claims 6 and 9 into claim 1. The presently claimed invention, therefore, now recites that the acylating agent is in a solution of the aprotic polar solvent and acid, and this solution is added to the peptide reaction mixture.

In view of the present amendment, the presently claimed process differs from Hansen as follows:

(a) In the presently claimed invention, less than 10%w/w of the aprotic polar solvent is present. Hansen describes a broad range of 17-83% (1/5-5/1) and exemplifies 66% (see Examples 6, 7, and 9).

(b) In the presently claimed invention, the acylating agent is dissolved in the polar aprotic solvent. Hansen doesn't describe or suggest this. In Example 6 of Hansen, the aprotic polar solvent is added to the aqueous peptide solution prior to the addition of the acylating agent.

(c) In the presently claimed invention, the acylating agent solution is stabilized with an acid. Hansen doesn't describe or even mention this. The only mention of acid in Hansen is for pH adjustment of the basic aqueous solution. This adjustment is performed prior to the addition of the aprotic polar solvent and the acylating agent (see page 11, lines 117-19) or after all of the reagents and solvents have been added (see Example 6). Using an acid to stabilize an acylating agent in an aprotic polar solvent is very different from merely adjusting the pH of a basic solution.

In addition, Applicants have shown that the presence of an acid as a stabilizing agent for the acylating agent/aprotic polar solvent solution provides an unexpected and highly beneficial result. Table 1, shown below, of the present application (see Example 6) shows that the presence of a stabilizing acid (e.g., $H_2SO_4$) significantly and unexpectedly reduces the presence of an impurity, α-glu, of the peptide acylation.

| Example # | Aqueous peptide solution (mL) | NMP added (mL) | NMP contents (%w/w) | $H_2SO_4$ added | α-glu |
|---|---|---|---|---|---|
| 1 | 23 | 0 | 0% | - | 0.5% |
| 2 | 23 | 1.7 | 7% | + | 0.4% |
| 3 | 25 | 1.8 | 7% | - | 4% |
| 4 | 23 | 6.8 + 1.7 | 28% | + | 0.5% |
| 5 | 20 | 100 + 1.4 | 84% | + | 14% |

Examples 2 and 3 show that the presence of an acid reduces the impurity by an order of magnitude (from 4% to 0.4%). Examples 2 and 4 show that even when the presence of the aprotic polar solvent is quadrupled, from 7 to 28%, the impurity level remains nearly the same (0.4% vs. 0.5%), which is an order of magnitude lower than the Example 3 (4%), which only has 7% aprotic polar solvent and no acid. Hansen simply did not appreciate the benefits of lowering the presence of the aprotic polar solvent and stabilizing the acylating agent/aprotic polar solvent with an acid. These changes, as shown above, provide significant and unexpected benefits.

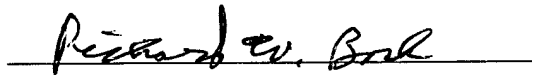
Zivanovic is unable to cure the deficiencies of Hansen. Zivanovic was cited merely to show that RP-HPLC would be obvious. This reference has nothing to do with acylating agent/aprotic polar solvent solutions or stabilization with an acid.

In view of the above, withdrawal of the obviousness rejection is respectfully requested.

The examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

Date: September 20, 2006



Richard W. Bork
Registration Number 36,459
Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540
(609) 987-5800

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